"Terlipressin-ephedrine versus ephedrine to treat hypotension at the induction of anesthesia in patients chronically treated with angiotensin converting-enzyme inhibitors: a prospective, randomized, double-blinded, crossover study."

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Abstract
In patients chronically treated with angiotensin converting-enzyme inhibitors (ACEI), typically selected doses of ephedrine do not always restore arterial blood pressure when anesthesia-induced hypotension occurs. We postulated that the administration of terlipressin, an agonist of the vasopressin system, with ephedrine more effectively restores pressure in this setting than the administration of ephedrine alone. This prospective, randomized, cross-over, double-blinded study compared terlipressin combined with ephedrine (n = 19) with ephedrine alone (n = 21) in treating hypotension at the induction of anesthesia in 40 ACEI-treated patients undergoing hypotension (mean arterial blood pressure [MAP] <65 mm Hg or <30% of baseline value) after standardized anesthetic protocol (target-controlled IV anesthesia with propofol). Data are mean +/- SD. Patient characteristics, MAP, and heart rate before and after the induction of anesthesia during hypotensive episodes were not significantly dif...

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Terlipressin-Ephedrine Versus Ephedrine to Treat Hypotension at the Induction of Anesthesia in Patients Chronically Treated with Angiotensin Converting-Enzyme Inhibitors: A Prospective, Randomized, Double-Blinded, Crossover Study

Karoline Meersschaert, MD*, Luc Brun, MD*, Maximilien Gourdin, MD*, Stéphane Mouren, MD, PhD†, Michèle Bertrand, MD*, Bruno Riou MD, PhD‡, and Pierre Coriat, MD* 

Departments of *Anesthesiology and Critical Care and †Emergency Medicine and Surgery, Centre Hospitalier Universitaire (CHU) Pitié-Salpêtrière, Assistance-Publique-Hôpitaux de Paris (AP-HP), Pierre et Marie Curie University, Paris, France; and ‡Department of Anesthesiology, Institut Mutualiste Montsouris, Paris, France

In patients chronically treated with angiotensin converting-enzyme inhibitors (ACEI), typically selected doses of ephedrine do not always restore arterial blood pressure when anesthesia-induced hypotension occurs. We postulated that the administration of terlipressin, an agonist of the vasopressin system, with ephedrine more effectively restores pressure in this setting than the administration of ephedrine alone. This prospective, randomized, cross-over, double-blinded study compared terlipressin combined with ephedrine (n/H1100519) with ephedrine alone (n/H1100521) in treating hypotension at the induction of anesthesia in 40 ACEI-treated patients undergoing hypotension (mean arterial blood pressure [MAP] /H1102165 mm Hg or /H1102130% of baseline value) after standardized anesthetic protocol (target-controlled IV anesthesia with propofol). Data are mean ± sd. Patient characteristics, MAP, and heart rate before and after the induction of anesthesia during hypotensive episodes were not significantly different between the two groups. After the first bolus, MAP was significantly greater in the Terlipressin-Ephedrine group (72 ± 12 mm Hg versus 65 ± 8 mm Hg, P < 0.05). The occurrence of a second hypotensive episode (5% versus 71%, P < 0.001), the duration (2 ± 1 min versus 3 ± 1 min, P < 0.01) of hypotensive episodes, and the median dose of ephedrine (3 versus 6 mg, P < 0.05) were significantly less in the Terlipressin-Ephedrine group. In conclusion, terlipressin combined with ephedrine is more effective than ephedrine alone for treating anesthesia-induced hypotension in ACEI-treated patients. We conclude that this patient population with a partially blocked endogenous response to hypotension may be good candidates for successful use of a vasopressin analog to counteract intraoperative refractory hypotension. 

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The sympathetic, renin-angiotensin, and vasopressin systems are important regulatory mechanisms for maintaining arterial blood pressure during circulatory challenges. Anesthesia interferes with the sympathetic system, inducing an angiotensin-dependence of the arterial blood pressure (1). Angiotensin converting-enzyme inhibitors (ACEI) are widely used as first-line therapy in arterial hypertension (2), but they alter the physiological mechanisms involved in arterial blood pressure regulation during anesthesia. ACEI therapy potentiates the hypotensive effect of anesthesia, which can lead to severe hypotension (3,4). Sympathetic adrenergic receptor agonists are considered the standard treatment for hypotension occurring at the induction of anesthesia (5,6), but their efficiency is limited in ACEI-treated patients (7). Angiotensin II restores arterial blood pressure in these conditions (8), but it is no longer available for clinical use. Because both sympathetic and renin-angiotensin systems are impaired by general anesthesia and

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Address correspondence and reprint requests to Pierre P. Coriat, MD, Department d’Anesthésie-Réanimation, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Boulevard de l’Hôpital, 75651 Paris Cedex 13, France. Address e-mail to pierre.coriat@psl.ap-hop-paris.fr. 

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chronic ACEI therapy, an agonist of the third neurohormonal system aimed at maintaining arterial blood pressure, the arginine vasopressin system, may be a more effective treatment for intraoperative hypotension in patients chronically treated with ACEI. Eyraud et al. (9) have shown that terlipressin, a synthetic analog of vasopressin, is effective in treating refractory hypotension in patients chronically treated by ACEI. However, terlipressin has not been compared with the standard treatment with ephedrine for anesthesia-induced hypotension. Therefore, we undertook a prospective, randomized, double-blinded, cross-over study to compare the effects of terlipressin combined with ephedrine and those of ephedrine alone in patients chronically treated with ACEI and experiencing hypotension at the induction of anesthesia.

**Methods**

After institutional ethical approval (CCPPRB Pitié-Salpêtrière) and written informed consent had been obtained, 42 patients undergoing vascular surgery and chronically treated by ACEI were included in the study. Forty of these patients experienced hypotension at the induction of anesthesia and were randomized and analyzed in the study. Anesthesia-induced hypotension was defined as a mean arterial blood pressure (MAP) <65 mm Hg or <30% of baseline value. Baseline value of MAP was the mean of two sets of measurements obtained at rest for 10 min at 24 h before surgery. Exclusion criteria were: age (<18 yr), emergency surgery, chronic treatment with ACEI for cardiac failure, chronic treatment with an angiotensin II receptor inhibitor, and anesthesia-induced hypotension associated with tachycardia (heart rate (HR) >90 bpm).

One hour before surgery, all patients received midazolam (5 mg *per os*) and their usual cardiovascular medications except ACEI. Five-lead electrocardiogram monitored patients with continuous ST segment analysis, invasive MAP, pulse oxygen saturation, and end-tidal CO₂. A catheter was inserted in the radial artery before the induction of anesthesia, and MAP was monitored throughout the study period.

A standardized induction technique was defined as: after the infusion of 10 mL/kg crystalloid, propofol was administered using a target-controlled total IV anesthesia device (Diprifusor®, Fresenius Vial SA, Brezin, France) to reach a target drug concentration of 3 μg/mL at the effect site in 1.5 min, 0.5 μg/kg of sufentanil, and 0.5 mg/kg of atracurium. After tracheal intubation, ventilation (tidal volume 10 mL/kg, ventilatory rate 12/min) was mechanically controlled with 2 L/min of fresh gas flow (N₂O/O₂ = 50%/50%) to maintain an end-tidal CO₂ (ETCO₂) between 30 and 35 mm Hg. Anesthesia was maintained with propofol (target concentration at the site effect 1.6 μg/mL). Only crystalloids were infused during the study.

In both groups, MAP and HR were recorded every minute until hypotension was corrected. All data were obtained before surgery. The patients were randomly assigned to one of two groups by opening an envelope just before the induction of anesthesia. Because this was a cross-over study, both treatment regimens were prepared. Terlipressin (1 mg in 5 mL of saline; Glypressine, Ferring SA, Gentilly, France), and placebo (5 mL of saline) were prepared in ready-to-use syringes outside the operating room by a nurse not involved in the care of the patient, and the syringes were blindly labeled (treatment A and B). Thus, terlipressin was prepared to allow the administration of a bolus of 1 mg in 5 mL. Ephedrine was prepared to allow the administration of a bolus of 3 mg in 1 mL (15 mg in 5 mL of saline). The syringes containing ephedrine were not blindly labeled. To restore MAP, terlipressin (or placebo) and ephedrine were simultaneously administered. Therefore, we compared terlipressin and ephedrine to ephedrine alone in the present study.

In both groups, the first episode of hypotension was treated with one bolus of ephedrine and one bolus of terlipressin or placebo (treatment A). If MAP was not restored (i.e., MAP was <65 mm Hg or <30% of baseline value) within 1 min, or if a second episode of hypotension occurred after the first regimen was repeated once. If MAP was not restored in 1 min after this second infusion, or if a third episode of hypotension occurred later, treatment B was initiated (cross-over) in the same manner (Fig. 1). In case of failure of both treatment A and B, additional boluses of ephedrine, norepinephrine (continuous IV infusion with incremental doses with an initial dose of 0.2 μg · kg⁻¹ · min⁻¹), or both could be administered by the attending anesthesiologist.

Hypertension was defined as a systolic arterial pressure more than 160 mm Hg. Blood samples for serum creatinine and cardiac troponin I measurements were withdrawn before surgery and during the three postoperative days.

Data are expressed as mean ± SD or median and a 95% confidence interval in non-Gaussian variables. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of variables. Comparison of two mean ± SD was performed using the unpaired Student’s *t*-test, and comparison of two medians was performed using the Mann-Whitney *U*-test. Comparison of percentages was performed using the Fisher’s exact test. All *P* values were two sided, and a *P* value of <0.05 was considered significant. Statistical analysis was performed on a computer using NCSS 6.0 software (Statistical Solutions Ltd, Cork, Ireland).
Results

Forty of the 42 enrolled patients completed the study. Two patients without hypotension at the induction of anesthesia were excluded from the analysis. No significant differences were observed between the groups in patient characteristics (Table 1), ACEI treatments (Table 2), or anesthetic management (Table 3). Baseline and preinduction MAP and HR were not significantly different between groups, nor were MAP and HR during hypotensive episodes (Table 4). The delays between the induction of anesthesia and the first hypotensive episode were 7 ± 5 min (n = 19) and 8 ± 9 min (n = 21), and 27 ± 14 min (n = 3) and 15 ± 11 min (n = 15) were the delays for the second hypotensive episode in the Terlipressin-Ephedrine and Placebo-Ephedrine groups, respectively, and were not significantly different between groups.

After the first bolus, MAP was significantly higher in the Terlipressin-Ephedrine group (Table 4). The number of patients requiring only one bolus to counteract hypotension was significantly larger in the Terlipressin-Ephedrine group (Fig. 2). The total duration of hypotension and the total dose of ephedrine were significantly less in the Terlipressin-Ephedrine group (Table 4).

Three patients in the Placebo-Ephedrine group and one patient in the Terlipressin-Ephedrine group were considered as failures because hypotension occurred despite two boluses. In the Placebo-Ephedrine group, hypotension was successfully treated in two patients using only one bolus of terlipressin-ephedrine, whereas hypotension persisted despite two boluses in the remaining patient. In the Terlipressin-Ephedrine group, hypotension persisted in only one patient despite two boluses of ephedrine alone. These two patients (one in the Placebo-Ephedrine group versus one in the Terlipressin-Ephedrine group) were considered to have refractory hypotension despite the four vasopressor infusions designed by the protocol. They received additional boluses of ephedrine, and MAP stabilized after surgical incision.

No hypertensive episode was observed before tracheal intubation. Hypertension occurred in five patients in the Terlipressin-Ephedrine group and in eight patients in the Placebo-Ephedrine group at intubation or surgical incision. The mean values of systolic arterial pressure (181 ± 14 mm Hg versus 173 ± 6 mm Hg, not significant) and HR (80 ± 8 bpm versus 79 ± 25 bpm) during these hypertensive episodes were not significantly different between groups. No significant changes occurred in the serum creatinine concentrations in the two groups over the three postoperative days. Cardiac troponin I concentrations remained within the normal range in all patients after surgery.

Discussion

Under anesthesia, the sympathetic, renin-angiotensin, and vasopressin systems are involved in the control of MAP, and each pressor system can act as a compensatory system when another system is depressed (1). ACEI-treated patients undergoing anesthesia are prone to develop hypotensive episodes after anesthetic induction (3,4) because the acute blockade of the sympathetic nervous system by anesthesia and the decrease in the loading condition of the heart provoked by anesthetics cannot be counterbalanced by a stimulation of the renin-angiotensin system, which would result in a vasopressin dependence of MAP (1,10,11). Agonists of the sympathetic system are used as standard therapy to counteract intraoperative hypotension (5,6) but may not always be effective in restoring MAP in patients with partially blocked endogenous response to hypotension (8,12). The blockade of the renin-angiotensin system attenuates the response to exogenous sympathetic agonists in patients treated by ACEI (13,14). In patients with chronic preoperative treatment with ACEI, anesthetic-induced hypotensive episodes are mainly attributed to decreased adrenergic vasoconstrictive response (15). This accounts for the decreased blood pressure response to agonists of the sympathetic system in anesthetized patients under ACEI therapy (7). Thus, more potent pharmacological drugs, acting through pathways other than the stimulation of α-adrenoceptors, may be required to treat refractory hypotension in such patients.

A vasopressin analog as a backup vasopressor has been firmly established to treat cardiac arrest and vasodilatory shock (16–19). In a recent study, arginine vasopressin was effective in reversing systemic hypotension in patients with catecholamine-resistant septic and postcardiotomy shock (20). In this study, arginine vasopressin was given in association with norepinephrine therapy (20). Consequently, we postulated that patients under chronic treatment with ACEI who undergo surgery with a partially blocked endogenous response to hypotension might benefit from successful use of an intraoperative vasopressin analog to restore blood pressure. Eyraud et al. (8) have demonstrated that a bolus of angiotensin II can restore the MAP with a concomitant decrease of serum creatinine concentration.
a vasopressin analog such as terlipressin could be a helpful alternative.

Terlipressin, or triglycylvasopressin, is a synthetic vasopressin analog that is converted into lysine-vasopressin, resulting in a prolonged arterial and venous vasoressor effect. A previous study from our group has shown that terlipressin was effective in correcting refractory hypotension by increasing peripheral vascular resistance without altering left ventricular function (9). However, a study comparing terlipressin and ephedrine was more effective than ephedrine alone for treating hypotension occurring at the induction of anesthesia in patients chronically treated by ACEI. Indeed, hypertensive episodes were more rapidly and more efficiently treated, and a second occurrence of hypotension was reduced in the Terlipressin-Ephedrine group compared with the Placebo-Ephedrine group. Interestingly, the combination of terlipressin with ephedrine restored blood pressure without increasing HR.

The efficiency of terlipressin after adrenoceptor agonists, as in the study of Eyraud et al. (9), or combined with adrenoceptor agonists, as in the present study, suggests that some interaction between ephedrine and terlipressin acting synergically on heart and vessels could have occurred. The synergic action between two agonists of two neurohumoral systems aimed at maintaining blood pressure and the potentiation of the simultaneous stimulation of two vasopressor systems have been established (13,14).

The correction of MAP with an unchanged HR might be beneficial in vascular patients with a high risk of coronary artery disease by increasing coronary perfusion pressure without any HR-induced increase in myocardial oxygen consumption. In addition, ephedrine and, to a lesser extent, terlipressin may act synergistically on left ventricular contractility and on the venous return to increase cardiac output (9,21–23). Finally, a synergistic effect of terlipressin and ephedrine on the intracellular calcium concentration of a vascular smooth muscle (24,25) can induce an increase in the peripheral vascular

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**Table 1. Characteristics of Patients**

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin-Ephedrine Group (n = 19)</th>
<th>Placebo-Ephedrine Group (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69 ± 7</td>
<td>66 ± 2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>71 ± 14</td>
<td>78 ± 12</td>
</tr>
<tr>
<td>Clinical history of ischemic heart disease</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Preoperative treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium blockers</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Nitrates</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Current smoking</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± sd or number (%). No significant differences between the two groups. NA = not applicable.

---

**Table 2. Angiotensin-Converting Enzyme Inhibitors Administered Chronically**

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin-Ephedrine Group (n = 19)</th>
<th>Placebo-Ephedrine Group (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benezepril</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enalapril</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Fozinopril</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Quinalapril</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Captopril</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Benezepril, Enalapril, Fozinopril, Lisinopril, Perindopril, Quinalapril, Ramipril, and Captopril.

---

The downside to the use of ephedrine is that repeated doses of this drug produce smaller sympathomimetic responses, which can lead to refractory hypotension (5). This led us to consider the need for activation of the arginine vasopressin system in association with ephedrine administration. We observed that a combination of terlipressin and ephedrine was more effective than ephedrine alone for treating hypotension occurring at the induction of anesthesia in patients chronically treated by ACEI. Indeed, hypertensive episodes were more rapidly and more efficiently treated, and a second occurrence of hypotension was reduced in the Terlipressin-Ephedrine group compared with the Placebo-Ephedrine group. Interestingly, the combination of terlipressin with ephedrine restored blood pressure without increasing HR.
resistances. In addition, some interaction between vaso-
pressin and ephedrine cannot be excluded. Indeed, ter-
lipressin increased α1 adrenoceptor responsiveness (26),
whereas an α-adrenergic stimulation may enhance the
terlipressin-induced vasoconstriction by increasing the
sensitivity of the vascular smooth muscle myofilaments
to calcium (27).

Several points must be considered in assessing the
relevance of our study. First, for methodological
reasons, the combination of terlipressin and ephed-
rine was used as one primary treatment rather than
ephedrine alone. However, the induction of anesthe-
sia in patients chronically treated with ACEI, and
terlipressin should only be used to treat refractory hypotension (1) and may be
responsive to standard treatment with ephedrine or α-adrenoceptor agonists. Thus, we consider that
adrenergic agonists should remain the first line at
therapy for hypotension at the induction of anesthe-
sia in patients chronically treated with ACEI, and
terlipressin should only be used to treat refractory hypotension, i.e., hypotension nonresponsive to two
or three infusions of adrenoceptor agonists. Second,
the present study demonstrated a benefit of terlip-
ressin combined with ephedrine. From the present
study, we cannot infer the effect of terlipressin alone
in this clinical setting. Third, our observation period
was limited to the preinduction and induction
phases of anesthesia, and the conclusions of the present study should not be extended to other por-
tions of the perioperative course. Further clinical
studies are required to elucidate these important
clinical issues and to establish the safety of a vaso-
pressin analog when given to counteract intraopera-
tive hypotension.

The potential downsides to the use of terlipressin
include an increased risk for postoperative hyperten-
sion, which did not exist in our study. It is also pos-
sible that the vasoconstrictor effect of terlipressin may
favor the development of a coronary artery spasm in
high-risk coronary artery disease patients or may de-
crease peripheral organ perfusion (splanchnic and re-
nal perfusion) in cases of hypovolemia. Those dele-
terious effects are counterbalanced by the restoration of
an adapted level of blood pressure, and they seem
unlikely if terlipressin is administered in hypotensive
patients chronically treated with ACEI in whom en-
dogenous vasoconstriction is partially blocked. How-
ever, our results cannot be extrapolated to other
patients.

In conclusion, our study confirms that hypotensive
episodes requiring vasoconstrictive treatment are fre-
quent after the induction of general anesthesia in pa-
tients chronically treated with ACEI. Hypotensive

### Table 3. Anesthesia and Fluid Loading Variables

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin-Ephedrine Group (n = 20)</th>
<th>Placebo-Ephedrine Group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anesthesia (min)</td>
<td>215 [140–290]</td>
<td>200 [150–290]</td>
</tr>
<tr>
<td>Duration of study period (min)</td>
<td>52 [40–63]</td>
<td>50 [40–70]</td>
</tr>
<tr>
<td>Preinduction volume loading (L)</td>
<td>0.7 [0.6–0.7]</td>
<td>0.7 [0.6–0.8]</td>
</tr>
<tr>
<td>Total volume loading of study period (L)</td>
<td>2.0 [1.5–2.5]</td>
<td>1.7 [1.0–2.0]</td>
</tr>
</tbody>
</table>

Data are expressed as medians [95% confidence interval]. There were no significant differences between groups.

### Table 4. Hemodynamics Variables

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin-Ephedrine Group (n = 19)</th>
<th>Placebo-Ephedrine Group (n = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before induction</td>
<td>92 ± 8</td>
<td>92 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Before first bolus</td>
<td>63 ± 5</td>
<td>62 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>After first bolus</td>
<td>72 ± 12</td>
<td>65 ± 8</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before second bolus</td>
<td>(n = 3)</td>
<td>(n = 15)</td>
<td></td>
</tr>
<tr>
<td>After second bolus</td>
<td>58 ± 7</td>
<td>60 ± 6</td>
<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before induction</td>
<td>69 ± 9</td>
<td>70 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>Before first bolus</td>
<td>57 ± 7</td>
<td>58 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>After first bolus</td>
<td>51 ± 12</td>
<td>56 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Total dose of ephedrine (mg)</td>
<td>3 [3–6]</td>
<td>6 [6–9]</td>
<td>0.05</td>
</tr>
<tr>
<td>Total duration of hypotension (min)</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or median [95% confidence interval]. No statistical comparison was performed at the second bolus because of the small sample size in the terlipressin-ephrine group (n = 3); n = 15 in the Placebo-Ephedrine group at the second bolus. NS = nonsignificant.
episodes may be unresponsive to ephedrine administration, and the combination of ephedrine and terlipressin is a more effective treatment of hypotension occurring in these patients. These results suggest that in a patient population under chronic treatment with ACEI who undergo general anesthesia with a partially blocked endogenous response to hypotension the use of a vasoconstrictor analog is helpful for maintaining intraoperative blood pressure.

Figure 2. Percentage of patients requiring one, two, or more than two boluses of vasoconstrictor to counteract hypotension in the Terlipressin-Ephedrine (n = 19) and Placebo-Ephedrine groups (n = 21). Patients who experienced more than two episodes were considered to be a failure and received the alternate treatment (cross-over).

References